Chronic High Altitude induced Apparent Diffusion Coefficient changes in Rat Hippocampus

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Target Audience: Researchers, Clinicians and Students.

Purpose: Ascent to high altitude often results in symptoms of acute mountain sickness (AMS) & if ignored, may lead to life threatening disease called high altitude cerebral edema (HACE). Previous studies have reported brain edema in patients suffering from AMS[1] as well as HACE[2]. Though it is uncertain whether cytotoxic edema or vasogenic edema predominates. There are limited reports on understanding water diffusion in brain in response to high altitude exposure. Diffusion Weighted Imaging is a powerful *in vivo* tool to understand water diffusion under pathophysiological conditions. Under the set of controlled environment, an ADC study on rat brain under chronic high altitude stress may help in setting new insights to address high altitude related problems effectively. This in turn can help in early risk assessment and studying new drug interventions to combat high altitude stress.

Objective: Examining edema in response to high altitude exposure

Materials and Method: Twenty one male Sprague Dawley rats (11-12 weeks old) were divided into 3 groups (7 rats each group). Group 1, 2 & 3 were exposed to hypobaric hypoxia at 22,000 feet for 7, 14, and 21 days respectively in climatic hypoxia chamber. Temperature & humidity were regulated at 25±1□C & 55±1% respectively. Diffusion weighted imaging imaging [DTIEPI sequence: TR/TE = 3800 ms/31ms, number of gradient encoding directions = 46, b= 670 s mm^{-2}, matrix = 128×128, field-of-view = 4cm, slice thickness=1 mm and number of slices=15 (contiguous)] experiments were carried out on rat brain before (baseline control) & after hypobaric hypoxia for each group on Bruker's small animal 7T MRI scanner. ADC calculation was done by placing ROI at CA1, CA2/3 and Dentate gyrus (Dg) using inhouse built JAVA based software.[3] Changes in ADC values of the regions of Hippocampus in response to hypobaric hypoxia was plotted against time and expressed as means ± SD (Fig-2). Changes in ADC values of each region between pre and post exposure for each group were compared separately by paired student's t-test using SPSS.

Results: ADC value of hippocampal tissue showed a decreasing trend. There was no significant change in ADC values after 7 days of chronic hypoxia. After 14 days of hypoxia CA2/3 and Dg showed a significant decrease in ADC values, while CA1 region did not show any significant change. CA1 showed a significant decrease after 21 days of hypoxia.

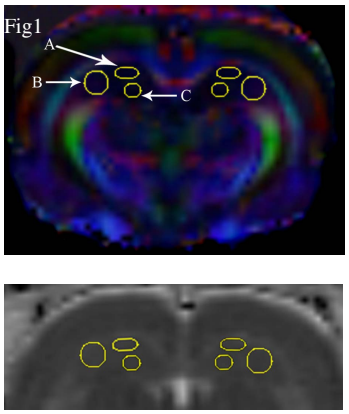

Fig1: Color coded FA map (upper), ADC map (lower) of rat brain showing placement of ROI's for ADC calculation: (A) CA1, (B) CA2/3 and (C) Dentate gyrus (Dg).

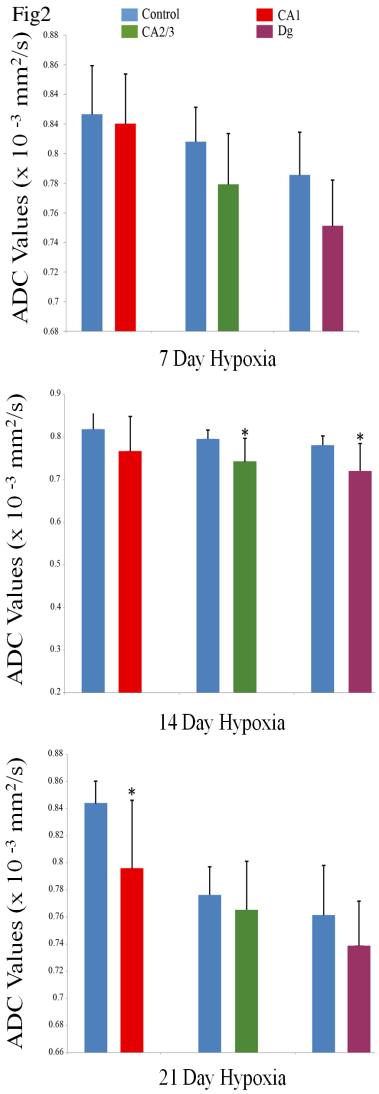

Fig2: ADC values of CA1, CA2/3 and Dg for pre (baseline control) and post chronic high altitude hypoxia exposure of 7, 14 and 21 days.
* statistically significant levels of P ≤ 0.05 w.r.t. pre-exposed baseline controls

Discussion: Previous reports on high altitude induced changes in hippocampus showed neurodegeneration in CA1 and CA3 region[4]. ADC results in present study also showed early changes in CA2/3 and Dg after chronic hypoxia exposure while CA1 region showed a delayed response. An observation of significant decrease in ADC values from CA2/3 and Dg after 14 days of high altitude exposure may be linked to cytotoxic edema. ADC gives an insight of diffusion of water within a tissue & its pathophysiological state. Decrease in ADC indicates entry of extracellular water into intracellular compartment in a tissue (cytotoxic edema). Present study showed decrease in ADC of CA1 region after 21 days of high altitude exposure. It may also be inferred from current study that CA2/3 and Dg regions are more prone to hypoxia induced changes at an early stage as compared to CA1 region of hippocampus.

Conclusion: Hippocampal regions showed restrictive water diffusion after exposure to chronic high altitude stress. Decrease in ADC value depicted cytotoxic edema indicating changes in tissue architecture at micro structural level. These results can further be correlated with other MR Imaging modalities, *invitro* High resolution NMR spectroscopy and histopathology study to detect early biomarkers for high altitude stress injuries in humans which can further be used for risk assessment, early diagnosis & developing interventions to combat high altitude stress.

References:

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